DRUG REPOSITIONING: AN OVERVIEW AND CLINICAL PERSPECTIVE

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Abstract:

The repositioning of drugs generates new use of a drug that already exists. It offers safe, reliable and faster treatment Drug position provides an additional advantage over new drug manufacturing as a result of reducing drug production costs as they have already been protected by safety and alternative measures, along with clinical trials. The flourishing position of medicines that holds an amazing future within the trendy medical sector can be stimulated by consciousness and inspiration. Exceptional improvements have been made in global standards, which will improve health care and nutrition. As there is clinical and pharmacokinetic evidence for current treatment, drug placement is a faster path of drug development. New approaches to the case of medicinal drugs, such as the reprocessing of patented medicinal products, would not be taken into account in the treatment of various diseases. This article focuses on drug pharmacology, pharmacodynamic, and safety profiles that are already known, undoubtedly allowing diagnostic studies to predominate.

Key Words: Drug Repositioning, Pharmacokinetics, Pharmacodynamic, Preclinical Studies.

Introduction:

Drug repurposing strategy placed the process of drug development on a fast track and has drawn researchers ' interest in a broader variety of scientific fields. In the field of repositioning, three main players can be identified, including academia and research institutes, pharmaceutical companies and technology companies that are being repurposed. Since in-vitro and in vivo available data on screening, complete chemical optimization, toxicity studies, Bulk processing, development of formulations and pharmacokinetics Drug profiles approved by the FDA, drug production cycles shortened as both of these essential steps can be circumvented. Furthermore, there is no need for greater investment and repurposed drugs are shown to be effective in preclinical models, thus falling slow destruction rates.[5] the key benefits of drug repurposing are therefore correlated with proven protection of the identified candidate drugs, dramatically shortened development time frames and costs associated with the candidate's advancement to clinical trials. Most of the repositioning drugs have been serendipitously found in the past. In addition to serendipitous findings, drug repurpositioning can be carried out using many techniques, including binding assays and phenotypic screening methods or computational methods as shown in table 1. In short, phenotypic methods include in-vitro and in-vivo tests while the obstacles include impact validation and deconvolution of targets. Network based methods, on the other hand, Discover new drug-disease relationships or high predictive precision drug-target relationships with limitations including inability to identify overlapping clusters.

A time-consuming, laborious, highly costly and high risk method is conventional drug discovery. In the conventional drug discovery programme, the innovative approach to drug repositioning has the ability to be used by mitigating high monetary costs, longer time of production and increased risk of failure It presents a reduced risk of failure when a failure rate of ~45 percent is associated with safety or toxicity problems in the conventional drug discovery programme, with the added advantage of saving up to 5-7 years in average drug development time. The drug repositioning strategy has gained significant traction in recent years, with around

one third of the new drug approvals corresponding to repurposed products that currently produce about 25 percent of the pharmaceutical industry's annual revenue. It has been stated that approximately 30 per cent of drugs and biologics (vaccines) approved by the US Food and Drug Administration (FDA) are repositioned drugs. The pharmaceutical industry has dramatically put the demand for repurposed drugs at $24.4 billion in 2015, according to recent figures, with expected growth of up to $31.3 billion in 2020. An accidental discovery / serendipitous observation in the 1920s were the first example of drug repositioning. More approaches to accelerating the process of drug repositioning have been established after about a century of progress. Sildenafil, minoxidil, aspirin, valproic acid, methotrexate etc. are some of the most popular and best known medications that have originated from the DR approach[7]. For example, sildenafil originally developed for the treatment of hypertension and angina pectoris has currently been used to treat erectile dysfunction.

Table 1. Overview on different drug repurposing approaches.

Repurposing approach	**Description**
Binding assay	Identify binding interactions of ligands to assay component
Phenotypic Screening	Evaluates a large number of authorized or evolving drugs in various prognostic models Evaluation of a series of compounds in an array of independent model
Pathway based or Network mapping Drug Centric	Involves constructing drug or disease networks based on gene expression patterns, disease pathology and protein interactions Uses structural information of the target site Examine effects of a single drug on multiple targets
Target based Knowledge-based Signature based	Identification of new indication based on drug's protein targets Consolidates known information about a drug anticipating unexplored biomarkers Based on the comparison of the unique characteristics or ‘signature’ of a drug against that of another drug, disease or clinical phenotype

The repositioning of drugs is possibly one of the most relevant tools for enhancing our natural science discovery and understanding, that can be a major research strategy, as many new medicines have high acceptance data concerning distribution, metabolism and excretion, clinical trial data previously expired, and post-Surveillance data for marketing these are more difficult and time-consuming to get.

Clinical development principles for drug repurposing:

Clinical research of a repurposed medication includes a comprehensive understanding of the basic pharmacokinetic / pharmacodynamic concepts of exposure, target binding and expression of functional pharmacological activity at the site of action. Some elements may have been elucidated for drug repurposing programmes during the production or acceptance of another indication that offers some measure of early risk reduction in both cost and time, An approved medication is tested on one end of the drug repurposing continuum at higher or lower doses than the maximum dose which is already approved by statutory agencies to target the similar molecular pathway / mechanism in a dissimilar patient group. The broad variety of clinical evidence and the knowledge gained in Phase III (efficacy) and Phase IV (post-marketing) trials for the drug in question provide a good understanding of its profile in terms of adverse events, long-term and chronic toxicity, and on- and off-label effects reducing the need for clinical trials in Phase I and Phase IIa / IIb, resulting in shorter development timelines. Moreover, even after

Identifying repurposed drugs, there are several challenges to overcome with objective: the precise dose, reaching the right compartment and to engage the correctly target, for the accurate time, in the right patient population, measured for the exact duration, with the correct tools/methodology.

Significance of drug repositioning:

They consist essentially of simplifying the regulatory procedures for bringing a previously approved drug onto the market.
This method takes into account earlier acquired facts, in exacting the safety and toxicity of the medication, which can significantly speed up the early progress phases of a repositioned medication. However, one significant factor is that, since the level of safety needed for a medication is highly dependent on its indication, the adverse effects of a medication would be reasonably less suitable when repositioned for a disease that is less serious or intense than its unusual indication
Drug Repositioning has two profiles: on target and off-target. In 'off-target' that aren't necessarily the ones they were originally intended to. But in reality, the drugs are completely 'on target' binding exactly to what they should bind. And it is not a positive thing when repositioning a medication. The concept of using a new dose, formulation or path administration, if medically appropriate. There are Systematic methods may also be broken down into approach and experimental method, additional and more commonly used.

Examples of repositioned drugs:

The scientific literature, as described, is full of studies aimed at demonstrating the utility of an existing drug in another indication, However, the *http:/drugrepurposing.info* website reports Drug repurposing Online was supplemented by 9859 compounds (although there is some overlap with on hand information) and new compound and mechanism interactions in 19082.

Minocycline

Minocycline has been in use since 1972, and is a semi-synthetic antibacterial analogue and has a broad-spectrum activity against a wide range of gram-positive and gramm negative bacteria. Susceptible species diseases and autoimmune conditions have medical uses. Its non-antibiotic activity has been demonstrated by many empirical studies, such as anti-inflammatory, inhibitor, anti-apoptotic, neuroprotective, and anti-cancer properties. The significant anti-inflammatory and immunomodulatory effects of Achromycin in the treatment of COVID-19 patients can lead to complications, particularly in the metabolic process, such as acute metabolic distress syndrome and multi-organ injury. In an excellent study conducted by, Achromycin prevented cytopathic effects from the human immunodeficiency virus (HIV). In addition, as reactivation in primary human CD^{4+} T cells, Achromycin decreased HIV replication in an excessively study. During this study, anti-HIV effects of Achromycin were found to be mediated by cellular environment change rather than direct drug-induced antiviral effects

Aspirin

For the treatment and prevention of atherosclerotic diseases, aspirin is widely used. COX-1 and COX- 2 are the pharmacological targets of aspirin COX-1 induce thromboxane A2 (TXA2) in platelets, which facilitates platelet aggregation and platelet adherence to tumour cells.
As a rapidly inducing enzyme during inflammation, COX-2 produces prostaglandin E2 (PGE2) predominantly in tumour cells as opposed to COX-1, and it is hypothesized that PGE2 plays an important role in promoting cell proliferation and tumour growth. Low (50-100 mg daily) and high (> 325 mg daily) doses of aspirin selectively block COX-1 and COX-2 irreversibly, respectively. In a tumour-bearing mouse in 1972, the anti-tumor effect of aspirin was first reported; supporting this evidence in a number of subsequent experimental studies, As seen in several clinical trials, a significant reduction in cancer risk and cancer-associated mortality has been seen in patients taking aspirin at a low dose. In the course of tumour suppression, COX-1 inhibition is the one significant mechanism of aspirin. Besides, PGE2 has been upregulated in colon cancer[19] and

angiogenesis[20]. PGE2 was significantly suppressed in human colons when aspirin was given even at a low dose (81 mg daily) [21]. PGE2 suppression may also be a significant factor in aspirin's anti-tumour action.

Chloroquine

To prevent or treat malarial infections, the 4-aminoquinoline agent Chloroquine (CQ) has been used and is subsequently used to treat discoid and systematic lupus erythematosus and rheumatoid arthritis. The dosage of chloroquine is largely based on the indication. Chloroquine is also marketed as chloroquine phosphate in 250 mg tablets, which corresponds to approximately 150 mg of chloroquine. For long-term use, the standard dose (rheumatoid arthritis and lupus) is 250 mg of chloroquine phosphate per day Chloroquine significantly reduced both tumour volume and tumour mass in a human melanoma xenograft model sample conducted by found that 25 and 50 mg / kg chloroquine doses both significantly improved survival time and decreased primary tumour volume in highly metastatic breast cancer cell mice

Nitroxoline

Nitroxoline, an old antibiotic, has been commonly used since the 1960s in countries such as Europe, Asia and Africa to treat urinary tract infections (UTI). Nitroxoline is quickly absorbed into plasma when ingested orally and is eventually excreted into urine Nitroxoline 's possible antibacterial activity mechanism is due to its ability to chelate divalent metal ions such as Mg^{2+} and Mn^{2+} In 2010, the anti-cancer activity of nitroxoline was initially reported. Several recent studies have also confirmed Nitroxoline's anti-cancer role. In a study performed the anti-cancer activity of nitroxoline against lymophoma, leukaemia, pancreatic cancer and ovarian cancer cells was shown. Nitroxoline has been used as a UTI medication in several European countries for over 50 years and no substantial human toxicity has been recorded, making it an excellent candidate for the repositioning of anti-cancer therapy.

Conclusion:

At the lighter note we want to conclude that the repurposing of medicines at any point of their developmental or clinical existence is a modern way of finding emerging technologies for existing drugs. It offers considerably improved pharmaceutical R&D efficiency on the basis of attritional risk, cost and development time parameters.

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Conflict of Interest:

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